JACC Vol. 11, No. 5
May 1988:1078–86

Compromise of Beneficial Effects of Reperfusion on Myocardium Supplied by Vessels With Critical Residual Stenosis

DONALD W. MYEARS, MD, RYUJI NOHARA, MD, DANA R. ABENDSCHEIN, PhD, JEFFREY E. SAFFITZ, MD, PhD, BURTON E. SOBEL, MD, FACC, STEVEN R. BERGMANN, MD, PhD

St. Louis, Missouri

Coronary thrombolysis in patients frequently unmasks high grade residual stenosis. To determine whether beneficial effects of reperfusion are compromised by critical residual coronary stenosis, 14 dogs were instrumented with an external left anterior descending coronary artery balloon occluder, Doppler flow probe and adjustable screw clamp. In eight of the dogs, critical stenosis (abolition of reactive hyperemia after a 20 s occlusion; 95.7 ± 1.0% cross-sectional area reduction) was induced before occlusion and maintained. In the control group (n = 6), no stenosis was induced. Each dog was subjected to 2 h of myocardial ischemia followed by balloon deflation and 24 h of reperfusion.

Myocardial blood flow assessed with microspheres was similar during balloon inflation in both groups and indicative of profound ischemia. Transmural blood flow to the reperfused zone assessed 1 min after balloon deflation was significantly greater in control dogs without residual stenosis (383% of normal compared with 120% of normal in dogs with stenosis) ($p < 0.01$). Compromise of transmural flow persisted in dogs with stenosis (85% compared with 121% of normal in control dogs after 1 h, $p < 0.05$; and 49% compared with 68% after 24 h of reperfusion, $p < 0.05$). Diminution of subendocardial blood flow after reperfusion was particularly marked. The extent of infarction was greater in the heart of dogs with residual stenosis.

Thus, residual critical coronary stenosis compromises nutritional perfusion and salvage of reperfused myocardium after recanalization. These observations underscore the need for prompt identification of patients with high grade residual stenosis early after coronary thrombolysis and the potential value of angioplasty or coronary surgery in selected patients soon after initial recanalization.

(J Am Coll Cardiol 1988;11:1078–86)

Coronary thrombolysis early after the onset of myocardial infarction salvages jeopardized myocardium, improves ventricular function and enhances survival (1–3). However, thrombolysis frequently unmasks a high grade residual coronary stenosis (4) that may limit reflow, attenuate otherwise beneficial effects of reperfusion and preclude substantial salvage of myocardium. Thus, emergency percutaneous transluminal coronary angioplasty or coronary artery bypass surgery may be required in selected subjects early after pharmacologically induced coronary thrombolysis when high grade residual stenosis is present. Unfortunately, the effects of residual stenosis on reflow and infarct size are not well defined. Reduced reflow and augmented infarct size have been reported (5) in experimental animals when reperfusion was induced through vessels with severe stenosis. In contrast, flow and infarct size after reperfusion have also been reported (6) to be uninfluenced by the presence of severe residual stenosis. The present study was performed to delineate the effects of reperfusion through vessels with residual critical coronary stenosis documented physiologically and anatomically on restoration of regional myocardial blood flow and salvage of ischemic myocardium.

Methods

Animal preparation. Twenty-four fasted mongrel dogs weighing 20 to 25 kg were premedicated with morphine sulfate (1 mg/kg body weight subcutaneously). Anesthesia was induced with thiopental (12.5 mg/kg intravenously) and maintained with alpha chloralose (90 mg/kg intravenously). All dogs were given 325 mg of aspirin orally 24 h before and

From the Cardiovascular Division, Department of Internal Medicine, Washington University School of Medicine, St. Louis, Missouri. This work was supported in part by SCOR in Ischemic Heart Disease Grant HL 17646 from the National Heart, Lung, and Blood Institute, Bethesda, Maryland.

Manuscript received September 3, 1987; revised manuscript received October 28, 1987, accepted December 14, 1987.

Address for reprints: Steven R. Bergmann, MD, PhD, Washington University School of Medicine, Cardiovascular Division, 660 South Euclid Avenue, Box 8086, St. Louis, Missouri 63110.

0735-1097/88/$3.50

again immediately before surgery to abolish platelet-induced cyclic coronary flow reductions that occurred invariably in pilot experiments when a critical stenosis was induced without pretreatment with aspirin. Animals were intubated and ventilated with room air. An aseptic left thoracotomy was performed in the fourth intercostal space, and the heart was suspended in a pericardial cradle. Catheters were placed in the right femoral artery and vein for monitoring aortic blood pressure and for administration of drugs and isotopes. A catheter was placed in the left atrium for administration of radiolabeled microspheres. The proximal left anterior descending coronary artery was dissected free and instrumented with a Doppler flow probe, adjustable screw clamp (4.4 mm wide renal artery clamp, Alko Diagnostic Corporation) and a pneumatic occluder. The screw clamp was anchored to the epicardium. The flow probe leads, occluder catheter and left atrial catheter were tunneled subcutaneously and exteriorized between the scapulae. Two dogs were instrumented with a radiolucent adjustable plastic sleeve in lieu of the metal screw clamp so that the severity of stenosis could be assessed angiographically. The thoracotomy was closed, the chest evacuated and the dogs condition stabilized during a 30 min interval.

Study groups. Two groups of dogs were studied: those with stenosis and control dogs without stenosis. In dogs with stenosis, the screw clamp or plastic sleeve was tightened before closure of the thoracotomy to abolish reactive hyperemia after a 20 s occlusion without compromising rest flow. In control dogs without stenosis, no tightening of the screw clamp was implemented. After stabilization, all dogs were given lidocaine (100 mg intravenous bolus followed by infusion of 1 mg/min) and subjected to 2 h of myocardial ischemia followed by 24 h of reperfusion. In each instance, interruption and restoration of flow in the left anterior descending coronary artery were verified with the Doppler flow probe.

Of the 24 dogs that underwent surgical instrumentation, 10 were excluded from analysis. These included six dogs that developed ventricular fibrillation after coronary occlusion, three dogs with a malfunctioning occluder and one dog whose rest flow was outside 2 standard deviations (SD) from the mean valve of normal flow for the whole group. Thus, 14 dogs (8 dogs with stenosis and 6 control dogs) served as the basis for this study. One dog in each group died during reinduction of anesthesia for the 24 h study, and thus data for blood flow at 24 h were unavailable for these two dogs. However, infarct size was quantitated. One dog in the stenosis group died overnight, and thus data for myocardial blood flow at 24 h and for infarct size were unobtainable.

Experimental protocol. Effects of balloon occlusion and its release on myocardial perfusion and metabolism were assessed sequentially in five dogs in each group by positron emission tomography after administration of oxygen-15–labeled H_2O ($H_2{}^{15}O$) and carbon-11–labeled palmitate (^{11}C-palmitate) during ischemia and 1 and 24 h after reperfusion. Regional myocardial blood flow was quantitated in absolute terms with radiolabeled microspheres in all dogs at the same intervals and, in addition, 1 min after the onset of reperfusion to define the influence of residual stenosis on reactive hyperemia. After completion of these initial studies, peripheral vascular catheters were removed, and the animals were given 600,000 units of penicillin and 750 mg of streptomycin intramuscularly and allowed to recover overnight. On the next day, dogs were anesthetized again and repeat tomographic data were acquired. Animals were then injected with 100 ml of 1% triphenyltetrazolium chloride intravenously. The heart was arrested with intravenous potassium chloride removed and rinsed with saline solution. In dogs with stenosis, the left anterior descending coronary artery was rapidly dissected free for assessment of luminal area. The heart was sectioned into 1 cm thick slices for further incubation in triphenyltetrazolium. Transmural samples of left ventricular myocardium were obtained from the central ischemic zone for assay of radioactivity associated with microspheres and from the normal posterolateral left ventricle for assay of radioactivity and myocardial creatine kinase activity.

Analysis of myocardial blood flow. Regional myocardial blood flow was measured with 15 μm radiolabeled microspheres (scandium-46, chromium-51, cerium-141 and strontium-85) using the standard arterial withdrawal reference technique. Flow was determined in samples taken from the ischemic and normal posterolateral regions from three ventricular slices subdivided into endocardial and epicardial layers.

Measurement of extent of infarction. Two independent methods were employed to assess the extent of myocardial infarction at necropsy. Sections of myocardium were placed in 1% triphenyltetrazolium at 37°C for 20 min immediately postmortem. The total area of left ventricular tissue and the area of myocardial infarction (triphenyltetrazolium negative tissue) were traced for each section. Total left ventricular and infarct surface area were determined by planimetry of each tracing. Infarct weight was determined by multiplying the weight of each section by the ratio of infarct area to total surface area; values were expressed as percent of left ventricular weight. Myocardial blood flow determinations were made for regions of interest in each section, after tracing had been completed. The entire heart was then frozen promptly for subsequent analysis of infarct size by measurement of creatine kinase content.

For determination of infarct size by the creatine kinase depletion technique (7), tissue samples used initially for analysis of flow were kept frozen while radioactivity was assayed, they were then added to the remainder of the heart before homogenization of the left ventricle. Creatine kinase per gram of left ventricle was compared with creatine kinase per gram in normal myocardium (obtained from assay of posterolateral samples). Infarct size was calculated as described previously (7) and expressed as a percent of left

JACC Vol. 11, No. 5
May 1988:1078–86

ventricular weight. No loss of creatine kinase activity was observed in absolute terms in samples of normal myocardium subjected to the triphenyltetrazolium incubation and counting procedures compared with activity observed in tissue assayed immediately postmortem (unpublished observation).

Tomographic assessment of myocardium at risk and region of injury. One dog in the control group and three dogs in the stenosis group could not be studied with positron emission tomography because of technical difficulties. Thus, five dogs from each group were evaluated with positron emission tomography. Each was placed in a plexiglass shell positioned within a tomograph (PETT VI) such that the entire left ventricle was within the field of view. Data acquisition was performed in high resolution mode (reconstructed full width at half maximum = 1.2 cm) with simultaneous acquisition of data for seven transverse sections and 1.4 cm separation between slices. Emission scans were corrected for attenuation and transmission data were acquired with an external ring source of gallium-68. For determination of myocardial perfusion, 35 to 40 mCi of $H_2{}^{15}O$ in saline solution was injected intravenously as a bolus. Data acquired during the interval from 10 to 50 s after injection were used to determine relative myocardial blood flow. Before acquisition of the $H_2{}^{15}O$ tomogram, approximately 60 mCi of oxygen-15–labeled carbon monoxide ($C^{15}O$) was administered by inhalation to label the blood pool used for correction of the $H_2{}^{15}O$ data for activity attributable to intravascular tracer. Approximately 10 min was required to permit decay of activity after acquisition of the $C^{15}O$ tomograms and before acquisition of the $H_2{}^{15}O$ tomograms. Composite $H_2{}^{15}O$ images corrected for intravascular tracer were analyzed in each tomographic section and summated for the entire left ventricle. Isocount contours representing 50% of peak myocardial counts were constructed for each section. The percent of myocardium with <50% of peak counts was defined as the region at risk.

After the $H_2{}^{15}O$ radioactivity had decayed to near background levels, an intravenous bolus of 15 to 20 mCi of ^{11}C-palmitate was administered and 10 consecutive 2 min images were collected beginning at the time of injection. The ^{11}C-palmitate image with maximal myocardial concentration of tracer corrected for intravascular tracer was analyzed and summated for the entire left ventricle. Isocount contours were constructed representing 50% of peak myocardial counts. The percent of myocardium exhibiting reduced metabolism (<50% of peak counts) was defined as the region of injury.

Quantification of coronary stenosis. Dogs with radiolucent plastic sleeves placed around the left anterior descending coronary artery underwent coronary angiography after tomography for measurement of luminal diameter and calculation of the reduction in vascular cross-sectional area. In the other dogs with stenosis, luminal area reduction was quantitated morphometrically. The excised segment of the artery with pneumatic occluder, flow probe and screw clamp intact was perfused for 2 h at 120 mm Hg with a solution of 10% phosphate-buffered formalin. After fixation, the instrumentation was removed, and the artery was cut transversely into 2 mm thick sections. Two sections from each of the three segments of the vessel (stenosed, normal proximal and normal distal) were embedded in paraffin and stained with hematoxylin-eosin. Areas were determined by planimetry, and the percent area reduction was expressed as a ratio of the average area in the stenotic region to the average area in the normal segments.

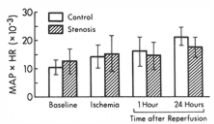


Figure 1. Rate-pressure product (mean arterial pressure [MAP] × heart rate [HR] ÷ 1,000) values are shown for both groups at each experimental interval. There are no significant differences between the groups at any time point, although heart rate tended to be greater in the control group 24 h after reperfusion.

Statistics. For comparisons of hemodynamic and myocardial blood flow values between groups, differences between values at selected time points and initial values were computed and analyzed with *t* tests. Repeated measures analysis of variance could not be utilized for comparisons because of violations of the equal variance assumption. Other intergroup comparisons were made with *t* tests for independent samples or chi-square analysis. Techniques for measuring infarct size were compared by using simple linear regression on the normally distributed data of infarct size values for both groups combined; p values < 0.05 were considered significant.

Results

Hemodynamics. There were no differences in mean arterial blood pressure, heart rate or heart rate-blood pressure product between groups with and without stenosis at baseline, during the interval of ischemia or 1 h after reperfusion. Twenty-four hours after reperfusion, mean arterial pressure was nearly identical in both groups, but control dogs exhibited a significantly higher mean heart rate (187 ± 17 compared with 159 ± 23 beats/min). Nevertheless, there was no significant difference in rate-pressure products between groups at any interval (Fig. 1).

Physiologic and anatomic severity of stenosis. Figure 2 depicts representative Doppler flow probe tracings indicative of reactive hyperemia after a 20 s occlusion of the left

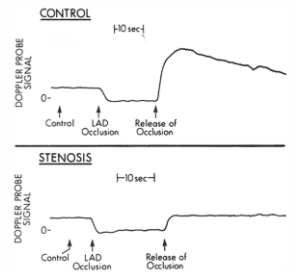


Figure 2. Representative Doppler probe signals are shown reflecting reactive hyperemia after a 20 s left anterior descending (LAD) coronary artery test occlusion. Reactive hyperemic flow in control dogs (**top panel**) was approximately four times rest left anterior descending coronary artery flow. However, in the dog with stenosis (**bottom panel**), reactive hyperemia was abolished, although rest flow was not affected.

anterior descending coronary artery in a control dog without stenosis and a dog with critical stenosis. Peak reactive hyperemic flow was approximately four fold greater than rest flow in control dogs, but absent in dogs with stenosis. Coronary angiography (Fig. 3) in two dogs with radiolucent stenosis documented luminal diameter reductions of 80% and cross-sectional area reductions of 96% for each. Planimetry of tracings of histologic sections of normal and stenotic left anterior descending coronary artery segments indicated a 95.6 ± 1.3% cross-sectional area reduction in the remaining dogs with stenosis (Fig. 3). Absolute cross-sectional area of the stenosis averaged 0.13 ± 0.05 mm^2.

Myocardial blood flow (Table 1). The reduction in blood flow induced by coronary occlusion was similar in both groups, although collateral flow during ischemia was slightly greater in dogs with stenosis compared with that in control dogs. Transmural flow to the anterior ischemic zone averaged 0.19 ± 0.08 ml/g per min (22% of normal flow) in control dogs and 0.25 ± 0.07 ml/g per min (30% of normal flow) in dogs with stenosis (p = NS). One minute after the onset of reperfusion, flow to the previously ischemic area was 4.06 ± 1.34 ml/g per min (383% of normal flow) in control dogs and 1.10 ± 0.47 ml/g per min (120% of normal flow) in dogs with stenosis ($p < 0.001$) (Fig. 4). Endocardial and epicardial zones exhibited concordant increases in flow immediately after reperfusion in control dogs (4.11 ± 1.37 and 4.00 ± 1.76 ml/g per min, respectively), but endocardial flow was disproportionately compromised compared with epicardial flow in dogs with stenosis (0.76 ± 0.40 versus 1.43 ± 0.60 ml/g per min, respectively; $p < 0.05$). One hour after the onset of

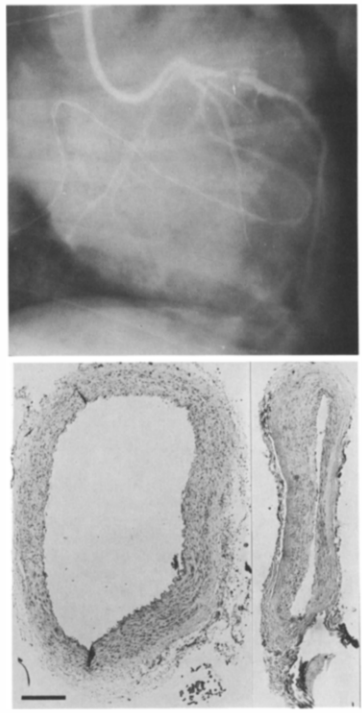


Figure 3. Top, Angiographic demonstration of the stenosis (**arrow**) in a dog that had a radiolucent plastic sleeve adjusted to abolish reactive hyperemia. **Bottom,** Six dogs had coronary stenosis induced by a metal clamp. Histologic sections in one dog obtained postmortem from proximal (**left**) and stenotic (**right**) regions of the left anterior descending coronary artery show the 95.6% cross-sectional area reduction induced by the intervention. The **solid bar** represents 0.25 mm.

reperfusion, transmural flow in reperfused myocardium had decreased in both group, but less so in control dogs (1.27 ± 0.26 ml/g per min, 120% of normal flow) than in dogs with stenosis (0.96 ± 0.45 ml/g per min, 92% of normal flow; p

Table 1. Myocardial Blood Flow After Induction of Ischemia and Reperfusion in Dogs With and Without Residual Coronary Stenosis

Group and Dog No.	During Ischemia (ml/g per min)						1 Min Postreperfusion (ml/g per min)					
	Ischemic			Normal			Ischemic			Normal		
	Endo	Epi	Trans	Endo	Epi	Trans	Endo	Epi	Trans	Endo	Epi	Trans
Stenosis												
1	0.08	0.31	0.20	0.83	1.09	0.96	X	X	X	X	X	X
2	0.12	0.42	0.27	1.11	1.14	1.12	1.42	2.16	1.79	0.88	0.92	0.90
3	0.14	0.37	0.26	0.96	1.06	1.01	X	X	X	X	X	X
4	0.08	0.28	0.18	0.54	0.56	0.55	0.33	0.86	0.60	0.67	0.60	0.64
5	0.12	0.13	0.12	0.56	0.47	0.52	0.61	0.55	0.58	0.64	0.48	0.56
6	0.18	0.41	0.30	0.83	0.78	0.80	0.83	1.66	1.24	1.10	1.06	1.08
7	0.09	0.57	0.33	0.82	0.85	0.84	0.41	1.63	1.02	1.07	1.02	1.04
8	0.17	0.47	0.32	1.00	0.91	0.96	0.98	1.74	1.36	1.29	1.25	1.27
Mean	0.12	0.37	0.25	0.83	0.86	0.84	0.76	1.43	1.10	0.94	0.89	0.92
±SD	±0.04	±0.13	±0.07	±0.20	±0.25	±0.22	±0.40	±0.60	±0.47	±0.26	±0.29	±0.27
Control												
1	0.15	0.30	0.22	0.72	0.74	0.73	4.79	2.72	3.76	0.71	0.69	0.70
2	0.07	0.18	0.12	0.97	0.99	0.98	3.05	3.70	3.38	1.20	1.11	1.15
3	0.28	0.34	0.31	0.97	0.95	0.96	5.98	4.03	5.00	1.28	1.23	1.26
4	0.04	0.17	0.10	0.70	0.72	0.71	2.84	3.24	3.04	0.75	0.77	0.76
5	0.01	0.25	0.13	0.95	0.88	0.92	2.85	2.88	2.86	0.97	0.97	0.97
6	0.16	0.32	0.24	1.10	0.88	0.99	5.17	7.45	6.31	1.49	1.55	1.52
Mean	0.12	0.26	0.19	0.90	0.86	0.88	4.11	4.00	4.06	1.07	1.05	1.06
±SD	±0.10	±0.07	±0.08	±0.16	±0.11	±0.13	±1.37	±1.76	±1.34	±0.31	±0.32	±0.31

DDI = died during induction; DO = died overnight; Endo = endocardial; Epi = epicardial; Trans = transmural; X = time points at which data could not be obtained for technical reasons.

versus control dogs < 0.05). One hour after the onset of reperfusion, endocardial flow remained differentially impaired in dogs with stenosis (81% of normal endocardial flow) compared with that in control dogs (124% of normal endocardial flow, $p < 0.05$) (Fig. 5).

Twenty-four hours after the onset of reperfusion, myocardial blood flow in reperfused tissue was decreased in both groups compared with flow 1 h after the onset of reperfusion. However, the decrease was significantly greater in dogs with stenosis (0.82 ± 0.39 ml/g/min, 48% of normal) than in control dogs (0.99 ± 0.44 ml/g/min, 68% of normal flow; $p < 0.05$). In addition, endocardial flow 24 h after reperfusion in dogs with stenosis remained depressed compared with corresponding values in cont[illegible] logs (33% compared with 62% of normal endocardial flo[illegible] < 0.05).

Risk region and the extent of infarction. There were no significant differences in risk region between dogs in the two groups. The risk region determined by positron emission tomography after administration of $H_2{}^{15}O$ averaged 23.8 ± 3.1% of the left ventricle in control dogs and 24.1 ± 4.2% in dogs with stenosis.

The distribution of infarct size determined at necropsy by analysis of myocardial creatine kinase depletion was bimodal in control dogs. Four hearts exhibited an infarct size of <6% of left ventricular mass and two infarcts were >19%; the average was 8.6 ± 8.8%. Infarct size was more uniform in dogs with critical, residual stenosis and averaged 13.1 ± 4.9% of left ventricular mass. Because of the nonparametric nature of the data a chi-square analysis was performed to determine whether the group with stenosis exhibited infarction that was ≥20% of the infarct size in control dogs. The results indicated that the median infarct size in dogs with stenosis (12.8% of the left ventricle) was statistically greater than the median in control dogs (3.5% of the left ventricle, $p < 0.05$). The correlation between infarct size estimated from creatine kinase depletion and by histochemical analysis after triphenyltetrazolium staining was close ($r = 0.95$) (Fig. 6). Similarly, the extent of injury assessed by ^{11}C-palmitate positron tomography correlated closely ($r = 0.89$) with infarct size determined at necropsy by analysis of creatine kinase depletion. The extent of infarction expressed as a percent of the risk region was lower in control dogs (40.9 ± 37.3%) than in dogs in the stenosis group (59.2 ± 30.4%), although the difference was not statistically significant because of the large variance.

Discussion

The results of this study indicate that a residual critical coronary stenosis impairs myocardial blood flow and limits salvage of myocardium after relief of occlusion. Thus they suggest that a high grade residual stenosis after pharmaco-

Table 1 (*continued*)

Group and Dog No.	1 h Postreperfusion (ml/g per min)						24 h Postreperfusion (ml/g per min)					
	Ischemic			Normal			Ischemic			Normal		
	Endo	Epi	Trans	Endo	Epi	Trans	Endo	Epi	Trans	Endo	Epi	Trans
Stenosis												
1	0.77	1.46	1.12	1.10	1.14	1.12	DDI	DDI	DDI	DDI	DDI	DDI
2	0.80	0.66	0.73	0.62	0.59	0.60	1.44	1.37	1.40	2.77	2.24	2.50
3	0.78	0.76	0.77	0.62	0.76	0.69	0.66	1.32	0.99	1.92	1.81	1.86
4	0.15	0.34	0.24	0.46	0.45	0.46	DO	DO	DO	DO	DO	DO
5	1.54	1.79	1.66	2.48	1.87	2.18	0.32	0.35	0.34	0.76	0.62	0.69
6	1.41	1.52	1.46	1.42	1.25	1.34	0.86	1.21	1.04	1.64	1.26	1.45
7	0.83	0.88	0.86	0.89	0.78	0.84	0.10	1.00	0.55	2.08	1.98	2.03
8	0.73	0.97	0.85	1.13	0.98	1.06	0.23	0.92	0.58	1.83	1.54	1.68
Mean	0.88	1.05	0.96	1.09	0.98	1.04	0.60	1.03	0.82	1.83	1.58	1.70
±SD	±0.43	±0.49	±0.45	±0.65	±0.45	±0.55	±0.50	±0.38	±0.39	±0.65	±0.58	±0.61
Control												
1	1.08	1.02	1.05	0.83	0.79	0.81	1.30	1.12	1.21	1.50	1.36	1.43
1	1.89	1.41	1.65	1.17	1.21	1.19	0.73	1.13	0.93	1.53	1.53	1.43
3	1.40	1.62	1.51	1.48	1.43	1.46	0.91	0.76	0.84	1.20	0.75	0.98
4	1.49	0.86	1.18	1.02	0.95	0.98	DDI	DDI	DDI	DDI	DDI	DDI
5	1.39	1.11	1.25	1.08	1.08	1.08	0.29	0.52	0.40	1.22	1.22	1.22
6	0.79	1.22	1.00	0.88	0.84	0.86	1.61	1.54	1.58	2.37	2.06	2.22
Mean	1.34	1.21	1.27	1.08	1.05	1.06	0.97	1.01	0.99	1.56	1.34	1.46
±SD	±0.37	±0.27	±0.26	±0.23	±0.24	±0.24	±0.51	±0.39	±0.44	±0.48	±0.47	±0.47

logic coronary thrombolysis in patients may impair restoration of nutritive blood flow and may also attenuate salvage of myocardium.

Methodologic considerations. Our initial plan was to obtain the data with chronically instrumented closed chest dogs that had fully recovered from surgery. However, results of pilot experiments consistent with the results of others (8) showed that extensive collateralization is induced by critical stenosis within 3 to 5 days, obviating the production of severe ischemia despite subsequent coronary occlusion. Accordingly, we studied dogs instrumented and evaluated on the same day, therefore, prolonged anesthesia was required. We did not evaluate the effects of residual stenosis on myocardial performance because it is clear that myocardial function is depressed for prolonged intervals after ischemia despite reperfusion.

Figure 4. Transmural myocardial blood flow to the zone (anterior) perfused by the left anterior descending coronary artery expressed as percent of normal zone flow. Both groups exhibited concordant reductions in transmural blood flow during the 2 h ischemic interval. However, 1 min after reperfusion, transmural flow in dogs with stenosis was severely compromised compared with that in control dogs. Transmural flow continued to be significantly impaired 1 and 24 h after reperfusion.

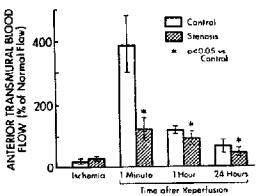
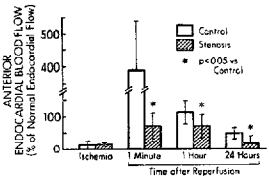


Figure 5. Endocardial blood flow to the perfused zone (anterior) by the left anterior descending coronary artery expressed as percent of normal endocardial flow. Endocardial flow was equally impaired in both groups during the ischemic interval. However, 1 min after reperfusion, endocardial flow in dogs with stenosis was < 20% of the value obtained in control dogs and continued to be compromised 1 and 24 h after reperfusion.



JACC Vol. 11, No. 5
May 1988:1078–86

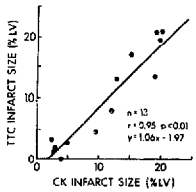


Figure 6. Correlation between infarct size as measured by creatine kinase (CK) depletion and as determined by planimetry of tracings of myocardial slices stained with triphenyltetrazolium (TTC). Infarct size could not be obtained in one dog in the stenosis group that died overnight. LV = left ventricle.

Our approach and results differ from those in previous studies that evaluated flow and extent of infarction. Schmidt et al. (5) assessed the impact of severe stenosis on infarct size after 2 h of ischemia and 4 h of reperfusion in dogs and found that infarct size was larger in dogs with stenosis compared with control dogs. However, reflow was initiated through a screw clamp that had been adjusted to provide only approximately 30% of rest flow on reperfusion. Accordingly, continued ischemia with more extensive infarction might be anticipated. Buda et al. (9) assessed myocardial blood flow and infarct size in open chest dogs subjected to ischemia for 2 h and reperfusion for 4 h. Subendocardial flow was compromised and infarct size was greater in dogs with a critical stenosis than in control dogs. However, infarct size in control dogs was more moderate than that in several studies (10–12) employing comparable durations of ischemia.

Conversely, Granato et al. (6,13) found no differences in myocardial blood flow after reperfusion in dogs with and without stenosis subjected to 1 or 3 h of coronary occlusion. However, neither immediate postreperfusion blood flow nor severity of stenosis was quantitated, and infarct size in dogs with ischemia for 3 h was not reduced at all by reperfusion in any group. No previous study has evaluated infarct size after 24 h of reperfusion.

Myocardial blood flow. Blood flow in the ischemic zone during coronary occlusion was slightly greater in dogs with residual stenosis than in control dogs. Despite the brief interval between induction of stenosis and occlusion, it is possible that the presence of the severe stenosis or the brief intervals of ischemia necessary to adjust the stenosis, or both, were sufficient to open existing collateral vessels more than was the case in dogs with coronary occlusion alone. However, the slight increase in flow during the interval of ischemia would presumably be "beneficial," resulting in decreased infarct size in contrast to the results actually obtained.

The maximal difference of flow between the two groups occurred immediately after the onset of reperfusion. Reactive hyperemia in dogs with critical stenosis was impaired markedly. Thus, distal coronary vasculature in these dogs was likely to be near maximally dilated even before the onset of occlusion. Otherwise rest flow would not have been normal in the presence of the proximal stenosis. Pilot studies in four additional dogs demonstrated that, at rest, no transmural flow gradient was induced by the critical stenosis. In contrast, control dogs had no "upstream" hindrance to flow or hyperemia immediately after onset of reperfusion; a nearly fourfold increase in flow occurred.

Transmural flow to reperfused myocardium expressed as a percent of normal zone flow was impaired not only immediately after the onset of reperfusion, but also 1 and 24 h later. Subendocardial flow was impaired disproportionately throughout the interval of reperfusion in dogs with critical stenosis. This disproportionate vulnerability may reflect the higher work load in the subendocardium and hence greater baseline vasodilation, as well as the greater wall stress and tissue pressure in this region (14). Preferential shunting of blood flow to epicardium may, therefore, occur in the setting of severe proximal stenosis after reperfusion.

Although impaired myocardial blood flow after reperfusion is likely to be deleterious, such may not be the case. Abrupt restoration of flow elicits changes in vascular endothelium and myocytes, referred to by some (15) as "reperfusion injury." Initial impairment of reflow induced by critical coronary stenosis may be paradoxically beneficial by attenuating oxyen free radical production and sarcolemmal damage secondary to accumulation of calcium. In a recent study by Yamazaki et al. (16), in which dogs were subjected to staged as opposed to sudden reperfusion after 3 h of myocardial ischemia, cardiac function improved and arrhythmias early after the onset of reperfusion were less marked in dogs with stenosis compared with control dogs.

Infarct size. Infarcts in both groups of dogs were subendocardial and patchy in nature. Thus, we assumed that determination of infarct size by creatine kinase depletion was likely to be more accurate than determination by triphenyltetrazolium staining. Nevertheless, results from both methods were similar. Dogs with residual critical coronary stenosis had a larger infarct in absolute terms and as a percent of risk region, and had a more uniform distribution of infarct size although baseline variables pertinent to infarct size (region at risk, collateral flow during ischemia and oxygen demand as estimated by the rate-pressure product) were comparable in the two groups.

Quantification of stenosis. A homogeneous and reproducible reduction in luminal cross-sectional area was accomplished. Values obtained with adjustable plastic sleeves were indistinguishable from those obtained with screw clamps.

The combined average value of 95.7 ± 1.0% area reduction agrees with data from others (17,18) with respect to "critical" stenosis (that is, severity such that a small additional reduction of luminal area reduces distal rest flow).

Clinical implications. Controversy surrounding the potential need for angioplasty or coronary surgery early after coronary thrombolysis has not been resolved. Some patients treated successfully with thrombolytic agents may be benefited. Some subjects exhibit high rates of reinfarction, recurrent ischemia or reocclusion (1,19,20)—often those with high grade residual stenosis technically amenable to angioplasty. Others may have occult excess injury to myocardium that could be ameliorated by more thorough recanalization. Angioplasty may relieve the relative subendocardial ischemia accompanying severe residual stenosis. This may be the mechanism responsible for the enhanced regional function and lower incidence of postinfarction angina observed in some patients treated with fibrinolytic agents initially and followed by early angioplasty (21). The recently reported results of the Thrombolysis and Angioplasty in Myocardial Infarction (TAMI) Trial (22) suggest that immediate angioplasty in patients with high grade residual stenosis after thrombolytic therapy is not warranted because myocardial function did not differ in patients with immediate compared with delayed angioplasty. However, delay of angioplasty in patients with successful thrombolysis but with high grade residual stenosis did lead to a higher incidence of emergency angioplasty or elective/urgent bypass surgery than was observed in patients undergoing immediate angioplasty. The lack of a salutary effect from early angioplasty may have been due to the duration (> 4 h) of antecedent ischemia in most patients because it has been demonstrated that metabolic recovery of myocardium after reperfusion does not occur when reperfusion is delayed after 4 h (12), and because functional recovery occurs only with restoration of oxidative metabolism (23,24).

Our results suggest that a residual critical coronary stenosis limits hyperemia otherwise induced by relief of total occlusion of 2 h duration, limits myocardial blood flow throughout the 24 h interval after the onset of reperfusion and reduces the salvage of jeopardized myocardium. They suggest a role for immediate angioplasty in patients who have initially successful pharmacologic thrombolysis early after the onset of ischemia and in whom high grade residual stenosis may impair endocardial blood flow and thereby limit maximal metabolic recovery, coronary flow reserve capacity and function.

We thank Bill Petty and Richard Rodriguez for technical assistance, David Marshall and the staff of the Washington University Medical Center Cyclotron for preparation of tracers, Ken Schechtman, PhD for statistical analysis and Becky Parnack and Barbara Donnelly for preparation of the manuscript.

References

1. Simoons ML, Serruys PW, van den Brand M, et al. Early thrombolysis in acute myocardial infarction: limitation of infarct size and improved survival. J Am Coll Cardiol 1986;7:717–28.
2. Sheehan FH, Braunwald E, Canner P, et al. The effect of intravenous thrombolytic therapy on left ventricular function: a report on tissue type plasminogen activator and streptokinase from the Thrombolysis in Myocardial Infarction (TIMI phase I) Trial. Circulation 1987;75:817–29.
3. Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI). Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction. Lancet 1986;i:397–401.
4. Rutsch W, Schartl M, Mathey D, et al. Percutaneous transluminal coronary recanalization: procedure, results, and acute complications. Am Heart J 1981;102:1178–81.
5. Schmidt SB, Varghese PJ, Bloom S, et al. The influence of residual coronary stenosis on size of infarction after reperfusion in a canine preparation. Circulation 1986;73:1354–9.
6. Granato JE, Watson DD, Flanagan TL, et al. Myocardial thallium-201 kinetics during coronary occlusion and reperfusion: influence of method of reflow and timing of thallium-201 administration. Circulation 1986;73:150–60.
7. Kjekshus JK, Sobel BE. Depressed myocardial creatine phosphokinase activity following experimental myocardial infarction in rabbits. Circ Res 1970;27:403–14.
8. Elliot EC, Bloor CM, Jones EL, et al. Effect of controlled coronary occlusion on collateral circulation in conscious dogs. Am J Physiol 1971;220:857–61.
9. Buda AJ, Gallagher KP, Wright LA, et al. Effect of critical stenosis on myocardial blood flow, ventricular function, and infarct size following coronary reperfusion (abstr). Circulation 1986;74(suppl II):II–18.
10. Knabb RM, Rosamond TL, Fox KAA, et al. Enhancement of salvage of reperfused ischemic myocardium by diltiazem. J Am Coll Cardiol 1986;8:861–71.
11. Karsch KR, Hofmann M, Rentrop KP, et al. Thrombolysis in acute experimental myocardial infarction. J Am Coll Cardiol 1983;1:427–35.
12. Bergmann SR, Lerch RA, Fox KAA, et al. Temporal dependence of beneficial effects of coronary thrombolysis characterized by positron tomography. Am J Med 1982;73:573–81.
13. Granato JE, Watson DD, Flanagan TL, et al. Myocardial thallium-201 kinetics and regional flow alterations with 3 hours of coronary occlusion and either rapid reperfusion through a totally patent vessel or slow reperfusion through a critical stenosis. J Am Coll Cardiol 1987;9:109–18.
14. Downey JM. Why the endocardium? In: Homrse DJ, Yellon DM, eds. Therapeutic Approaches to Myocardial Infarct Size Limitation. New York: Raven Press, 1984:125–38.
15. Nayler WG, Elz JS. Reperfusion injury: laboratory artifact or clinical dilemma? Circulation 1986;74:213–21.
16. Yamazaki S, Fujibayashi Y, Rajagopalan RE, et al. Effects of staged versus sudden reperfusion after acute coronary occlusion in the dog. J Am Coll Cardiol 1986;7:564–72.
17. Elzinga WE, Skinner DB. Hemodynamic characteristics of critical stenosis in canine coronary arteries. J Thorac Cardiovasc Surg 1975;69:217–22.
18. Nichols AB, Brown C, Han J, et al. Effect of coronary stenotic lesions on regional myocardial blood flow at rest. Circulation 1986;74:746–57.
19. O'Neill W, Timmis G, Bourdillon PDV, et al. A prospective randomized clinical trial of intracoronary streptokinase versus coronary angioplasty therapy for acute myocardial infarction. N Engl J Med 1986;314:812–8.
20. Schaer DH, Ross AM, Wasserman AG. Reinfarction, recurrent angina, and reocclusion after thrombolytic therapy. Circulation 1987;76(suppl II):II-57–62.
21. Topol EJ, O'Neill WW, Langburd AB, et al. A randomized, placebo-

controlled trial of intravenous recombinant tissue-type plasminogen activator and emergency coronary angioplasty in patients with acute myocardial infarction. Circulation 1987;75:420–8.

22. Topol EJ, Califf RM, George BS, et al. A randomized trial of immediate versus delayed elective angioplasty after intravenous tissue plasminogen activator in acute myocardial infarction. N Engl J Med 1987;317:581–7.

23. Schwaiger M, Schelbert HR, Ellison D, et al. Sustained regional abnormalities in cardiac metabolism after transient ischemia in the chronic dog model. J Am Coll Cardiol 1985;6:336–47.

24. Taegtmeyer H, Robert AFC, Raine AEG. Energy metabolism in reperfused heart muscle: metabolic correlates to return of function. J Am Coll Cardiol 1985;6:864–70.